Published in final edited form as:

J Urol. 2019 May ; 201(5): 868–870. doi:10.1097/JU.0000000000000049.

INFLAMMATION, VOIDING AND BPH PROGRESSION

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Keywords

Benign Prostatic Hyperplasia; BPH; Inflammation; Lower Urinary Tract Symptoms; LUTS;
Prostate; Voiding

Introduction

Lower urinary tract symptoms (LUTS) impact the lives of millions of men, often as a consequence of benign prostatic hyperplasia (BPH), a histologic diagnosis that refers to the proliferation of glandular and stromal elements, smooth muscle activity, and connective tissue within the prostatic transition zone. Parallel to this anatomical and functional interplay, LUTS increase in frequency and severity with age.

However, the factors that underlie BPH remain poorly defined, and even more so their interaction with LUTS. Regardless of the physical size of the gland itself, the most common pathway that causes men to enter the realm of prostate medication and procedures is LUTS.

Evidence for a two-factor model of LUTS exists: bulk growth and adrenergically-driven smooth muscle tone that interfere with voiding. Inflammation, in many forms, interacts with LUTS but its definition and role is unclear. Our goal herein is to explore the impact of inflammation on the clinical endpoints of both physical prostate size, as well as symptoms as reflected by the International Prostate Symptom Score (IPSS).

Prostate-specific Inflammation

At the level of the prostate, histologically-identified inflammation is a common finding in tissue resected from men with symptomatic BPH. First in 1979, 98% of TURP specimens were observed to have inflammation, and subsequent surveys found presence of

inflammation using varied histologic criteria to range from 43–100%. Increasing size of gland appears related to likelihood of inflammation being present in some series. A consensus definition of histologic findings was subsequently generated in an attempt to organize the thought and reporting of inflammation within the tissues of the prostate. Further confounding the topic, inflammation may be defined in many ways: the most commonly reported form in prostate tissue is the presence of immune cell infiltrates, but cellular inflammatory markers including CD-4, CD-8, CD-45 and CD-68 as well as tumor necrosis factor, interleukin-6 and others have all been evaluated, and with varied findings.

Do men without symptoms have prostate inflammation as well? Placebo controlled drug trials have helped fill gaps created by studying tissue only from men who had required surgery. The REDUCE trial assessed the impact of dutasteride on prostate cancer over a 4-year interval; MTOPS looked at BPH progression over 4.5 years. Both of these large trials included baseline biopsies for all patients included, 1198 men in the MTOPS series and 8824 men in REDUCE, allowing post-hoc assessment of inflammation in the prostate. These data found inflammation correlated with an increase in measured size of 4.3 additional grams in the MTOPS study, and 3.1g additional size in the REDUCE placebo arm. When looking at IPSS, the REDUCE patients reported a higher score by 0.6 IPSS points (8.8 vs 8.2) while the MTOPS patients showed no difference in IPSS scores. Although there does appear to be a relationship between these measures of prostate-level inflammation and BPH/LUTS, this small difference in prostate volume and IPSS leads one to wonder about its clinical relevance.

An important feature of the inflammatory landscape is the recurring finding of association between the presence of inflammation in the prostate and increased risk of acute urinary retention (AUR). MTOPS found that 5.6% of patients with prostate inflammation at baseline progressed to AUR, while none of the patients lacking inflammation had subsequent progression to AUR. Analysis of intraprostatic levels of inflammatory marker CD-8 found that those in the highest tertile experienced a 3.64 HR for AUR despite no increased baseline IPSS.⁴ Another study found that a higher proportion of TURPS done for AUR had inflammation present than those performed for symptoms alone. Whether AUR represents a culmination of ongoing decline in voiding function, or is a result of acute inflammatory process is unknown, but it does seem clear that intraprostatic inflammation is associated fairly specifically with AUR.

Systemic Inflammation

Systemic inflammation interacts with LUTS in ways that may not involve the prostate. One avenue to evaluate this interaction is by observing the impact of widely used non-steroidal anti-inflammatory medications (NSAIDs). Observational data regarding the impact of NSAIDs on LUTS are variable. The 1990 Olmstead County cohort found long-term usage of NSAIDs associated with a lower chance of LUTS or decreased flow rate. Conversely, a population-based case-control study from the Netherlands suggested that NSAID usage was associated with a two-times higher risk of acute urinary retention, and analysis of 4,735 American men found an increased BPH/LUTS with NSAID usage. Data from a separate

4771 men found no association between NSAID usage and 6 different clinical definitions of BPH/LUTS.¹

Interventional studies with NSAIDs do suggest a temporary benefit. Two smaller randomized controlled trials showed certain NSAIDs hasten IPSS improvement and flow rate compared to alpha-blockade or finasteride alone, and a meta-analysis found that NSAIDs, when given over periods of 4–24 weeks, improved symptoms by 2.9 IPSS points and flow by 0.89 ml/sec.² What mechanisms mediate this effect, systemically and/or in the prostate itself, remain unknown.

A different and interesting assessment of systemic inflammation is serum C-reactive protein levels: this acute-phase protein is associated with a wide variety of inflammatory states. CRP is predictive of residual LUTS in men after medical treatment of voiding symptoms, independently of prostate size or other identifiable parameters. When women as well as men are studied, risk of increased IPSS score with higher CRP is still seen regardless of gender. Markers of systemic inflammatory processes appear to interact with LUTS independent of prostate presence.³

Summary

In which men are LUTS driven by systemic inflammatory factors, prostate-specific changes, or both? Is prostatic inflammation a meaningful aggregation of irritative and pro-growth processes and a key step towards hyperplasia and intervention, or merely an insignificant passenger finding that occurs with ageing and gland enlargement? The literature suggests that inflammation localized to the prostate predicts AUR, but its importance to BPH and LUTS is much less clear.

An IPSS change of 3 is at the border of patient perception, and while large groups of well-studied patients do show an increase in IPSS score in the presence of inflammation, it is well below this clinically relevant change. Similarly, differences in prostate size with and without inflammation appear real in REDUCE and MTOPS, but the incremental increases of 3.1g and 4.3g are unlikely to be clinically significant. Inflammation does appear to significantly increase the chance of acute urinary retention, a separate endpoint.

Better research with the goal of identifying and defining phenotypes of men with LUTS is necessary. A man with an IPSS score of 20 may experience symptoms as a consequence of BPH and local obstruction, or systemic inflammatory processes that interact with voiding in very different ways. These will very likely respond to different treatments. In serum alone, there are suggestions that different markers of inflammation relate to different outcomes. Other clues that may lead to phenotypic grouping exist: one recent study suggested that inflammation occurring in stromal vs non-stromal prostatic tissue compartments are different, including a 10-gram difference in prostate size and higher voiding pressures.⁵ Much work remains to define the patterns and definitions of prostatic or systemic inflammation within the complex ecosystem of urinary symptoms, gland size, BPH progression and AUR.

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